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Can Folic Acid Protect against Congenital Heart Defects in Down Syndrome?

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BACKGROUND: Several studies have suggested a protective effect of folic acid (FA) on congenital heart anomalies. Down syndrome (DS) infants are known to have a high frequency of heart anomalies. Not all children with DS suffer from heart anomalies, which raises the question whether maternal factors might affect the risk of these anomalies. Our objectives were to investigate whether first-trimester FA use protects against heart anomalies among DS children. **METHODS:** Women with liveborn DS children participating in the Slone Epidemiology Center Birth Defects Study between 1976 and 1997 were included. We performed case-control analyses using DS, with heart anomalies as cases and DS, without heart anomalies as controls. Subanalyses were performed for defects that have been associated with FA in non-DS populations (conotruncal, ventricular septal [VSD]) and for those that are associated with DS (ostium secundum type atrial septal defects [ASD] and endocardial cushion defects [ECD]). Exposure was defined as the use of any FA-containing product for an average of at least 4 days per week during the first 12 weeks of pregnancy, whereas no exposure was defined as no use of FA in these 12 weeks. **RESULTS:** Of the 223 cases, 110 (49%) were exposed versus 84 (46%) of the 184 controls. After adjustment for possible confounders, no protective effect of FA was found on heart anomalies overall (OR 0.95, 95% CI: 0.61–1.47) nor separately for conotruncal defects, VSDs, ASDs, or ECDs. **CONCLUSIONS:** Our study does not show a protective effect of FA on heart anomalies among infants with DS. *Birth Defects Research (Part A) 76:714–717, 2006.* © 2006 Wiley-Liss, Inc.

Key words: Down syndrome; folic acid; heart anomalies; birth defects; case-control study

INTRODUCTION

Although clinical features of Down syndrome (DS) are well recognized, it remains unclear how the extra chromosome relates to the high incidence of certain major malformations among DS children compared to the unaffected population. For example, cardiac malformations are commonly seen among DS infants, with incidence rates varying between 40 and 50%. Shapiro (1983) suggests that besides direct effects of the chromosomal abnormality, it might be possible that maternal risk factors interact with an already susceptible genotype, leading to the development of major anomalies in some individuals but not in others.

Studies on maternal risk factors and major birth defects restricted to infants with DS are few and results are not consistent, but there is some evidence that environmental factors might influence the occurrence of defects among fetuses with an extra chromosome 21. For maternal age, findings differ on the direction of risks: while Källèn et al. (1996) found that DS infants born to teenage mothers had a decreased risk for cardiac defects, which was particularly pronounced for endocardial cushion defects (ECDs) and ventricular septum defects (VSDs), they also found an increased risk for megacolon for mothers <25 years of age. Khoury and Erickson (1992) also found an inverse association, but with maternal age and oral clefts; additionally, they found an association between maternal race and cardiac defects (40% among blacks vs. 17% in whites).

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With respect to exogenous factors, Fixler and Threlkeld (1998) found no differences in risk of heart defects in relation to maternal illness, medication use, or consumption of caffeinated beverages, cigarettes, or alcohol, but others did find an effect of such maternal exogenous exposures. Khoury and Erickson (1992) found an association between first-trimester fever and duodenal atresia. Although this was not confirmed in a later study by Torfs and Christianson (1999), the latter did find associations between coffee consumption and maternal fever and Hirschsprung's disease as well as between smoking and cardiac defects; alcohol was not associated with any defect. Taken together, these studies suggest maternal factors might play a role in the origin of major congenital anomalies among infants with DS.

No study, however, has evaluated the risks of major birth defects among DS affected infants in relation to maternal use of folic acid (FA). In the general population, studies suggest that FA use may reduce the risk of cardiac defects. While Werler et al. (1999) found no association between multivitamin use and conotruncal defects or VSDs, other studies did find evidence of such an association. In a randomized clinical trial, Czeizel (1998) found a significant protective effect of FA-containing multivitamins for heart defects overall (odds ratio [OR] 0.42, 95% confidence interval [CI] 0.19–0.98) and for conotruncal defects [OR] 0.29, 95% CI 0.09–.097) in particular. A number of observational studies were consistent with that finding. For example, Botto et al. (2000) found significant protective effects of multivitamins (which usually contain FA) on outflow tract defects, VSDs, and cardiac defects overall. Furthermore, studies of Hernandez-Diaz et al. (2000) and Meijer et al. (2005) provide indirect evidence of a possible protective effect of FA on cardiac defects. Both found an increased risk of cardiac defects after intrauterine exposure to medications that antagonize the effects of FA; this risk diminished if FA supplements were taken along with the FA antagonists (Hernandez-Diaz et al., 2000). Although these studies did not investigate the effect on heart anomalies specifically among DS affected infants, their results raise the question of whether FA might reduce the risk of heart anomalies in this particular population. We therefore sought to evaluate the hypothesis that FA has a protective effect on heart anomalies among infants with DS.

MATERIALS AND METHODS

Since 1976, the Boston University Slone Epidemiology Center Birth Defects Study (BDS) has been interviewing mothers of children with a range of birth defects (Mitchell et al., 1981). Until 1997, mothers from the areas around Boston (since 1976), Philadelphia (since 1977), and Toronto (since 1978) were interviewed in person, within 6 months of delivery, usually in the subject's home, by a trained study nurse. Because of personnel limitations, not all eligible subjects were approached for interview. Rather, those subjects that were approached were selected based on ''priority'' diagnoses that reflected changing research interests of the program. For example, from 1983 to 1987 DS was on the priority list but neural tube defects (NTDs) were not. From 1988 to 1992, NTDs were on the priority list, but DS was not. Therefore, during the latter period, all subjects with an NTD and only a sample of those with DS were approached for interview. However, selection of subjects for interview was never dependent on exposure to any particular agent. The interview contained questions about demographic, reproductive, and medical factors, as well as details about all medications used, including vitamins. The product name, starting and stopping dates, and frequency of use were recorded for each vitamin product taken between 2 months before through the end of pregnancy.

The present analyses include data on liveborn infants with DS enrolled between 1976, the start of the study, and 1997, the year before food fortification with FA. We excluded infants with gestational age <37 weeks whose only cardiac anomaly was patent foramen ovale, ostium secundum type atrial septal defects (ASD), or patent ductus arteriosus ($n = 15$). Among the remaining 773 DS infants, cases were defined as infants with any heart anomaly. Separate analyses were performed for conotruncal defects, VSDs, ECDs, and ASDs. The first 2 defects were included because of the inverse association with FA in the literature and the latter 2 because they are commonly seen among DS infants. The four groups were not mutually exclusive. Controls were DS infants without a heart anomaly.

Since lunar months 2 and 3 are most important regarding development of heart anomalies, exposure to FA was defined as the use of any FA-containing product for at least 48 days during the first 12 weeks of pregnancy (lunar months 1–3), which corresponds to an average of 4 days per week during this period. In all exposed study subjects, the exposure occurred on ≥16 days in lunar months 2 and 3. No exposure was defined as no FA use at all in these first 12 weeks of pregnancy.

Multivariate models were used to calculate adjusted ORs and 95% CIs. Variables that were related to exposure and/or outcome were included in the model: maternal race (white/nonwhite), maternal age (<25, 25–29, 30–34, and >34), maternal education (<12, 12, 13–15, and >15 years), maternal diabetes (yes/no), year of birth (<83, 83–87, 88–92, and >92), and geographic center (Boston, Philadelphia, and Toronto).

RESULTS

Of the 773 DS affected infants in the database, 366 were excluded because the mothers used FA but at frequencies and durations that were inadequate to meet the exposure criteria. Among the 407 who met these criteria, 223 (55%) were cases and 184 (45%) were controls. The cases included 20 births with conotruncal defects, 73 with VSD, 73 with ASD, and 85 with ECD. Among the excluded births, a similar distribution of cases and controls was found (58% cases).

The characteristics of the cases and controls are shown in Table 1. Among cases, more mothers reported never having smoked and more had diabetes, whereas fewer mothers were White and fewer infants were male (all $P < .05$). There was little difference between cases and controls for maternal age, education, parity, alcohol drinking, or whether the pregnancy was planned.

Of the 223 cases, 110 (49%) were exposed to FA, versus 84 (46%) of the 184 controls. Logistic regression that adjusted for race, maternal age, maternal education, maternal diabetes, year of birth, and center of birth revealed no protective effect of FA for heart anomalies overall (OR 0.95, 95% CI 0.61–1.47), as is shown in Table 2. Maternal FA use was also not associated with any of the 4 cardiac subgroups; ORs showed some variation, but none of the CIs excluded 1.0.

Table 1
Characteristics of Cases and Controls

	Controls ($n = 184$)		Heart anomaly ($n = 223$)	
	n	%	*n*	%
Smoking[b]				
Never	76	41.3	118	52.9
During (part of) pregnancy	67	36.4	48	21.5
Exsmoker	41	22.3	57	25.6
Alcohol during pregnancy[a]				
Yes	33	20.2	49	23.7
Missing $n = 37$				
Material race[b]				
White (vs. non-White)	171	92.9	192	86.1
Material age at conception				
<25	32	17.4	37	16.6
25–29	55	29.9	69	30.9
30–34	56	30.4	55	24.7
>34	41	22.3	62	27.8
Maternal years of education				
<12	23	12.5	27	12.1
12	53	28.8	63	28.3
13–15	59	32.1	57	25.6
>15	49	26.6	76	34.1
Planned pregnancy[a]				
Yes	102	62.6	132	64.7
Missing $n = 40$				
Maternal diabetes[a,b]				
Yes	3	1.6	13	5.9
Missing $n = 4$				
Parity				
Primipara	42	22.8	51	22.9
Sex of baby[b]				
Male	124	67.4	105	47.1
Center				
Boston	65	35.3	67	30.0
Philadelphia	55	29.9	58	26.0
Toronto	64	34.8	98	43.9

[a]If missing data: percentages calculated on available data.
[b]Significant difference between cases and controls ($P < .05$).

DISCUSSION

In this study, we examined whether the risk of congenital heart defects among DS affected infants is decreased by first trimester FA exposure. The literature provides some support for such an effect in the general population, particularly with respect to conotruncal defects and VSDs. However, the present data do not provide evidence for a protective effect of FA on the occurrence of heart anomalies overall among DS affected infants, nor for the subgroups of conotruncal defects, VSDs, ASDs, or ECDs.

The strength of this study is that we only included children born to mothers who took FA regularly or did not take FA at all. By eliminating occasional FA users, our approach maximized the opportunity to identify a protective effect of FA on heart anomalies among DS infants.

Nevertheless, several limitations of the present study should be considered. Because data about exposure are collected after birth, information bias could occur. We attempted to minimize such bias by using standardized questionnaires and by conducting the interviews relatively soon after the infant's birth. By using other DS affected infants as controls, we attempted to avoid recall bias, a specific type of information bias.

Not all infants with DS encountered in the study hospitals were enrolled in the study because DS was only on the priority list between 1983 and 1987. In the other years, many infants with DS were enrolled not because of the specific diagnosis of DS, but rather because of the presence of other malformations. However, there is no reason to assume that recruitment of subjects was related to use of FA-containing products, making it unlikely that this process introduced selection bias. Another possibility is that defects that may be FA-sensitive (such as neural tube or urinary tract defects) were included in the control group. However, the numbers of such defects among controls were small, and the proportions of DS affected infants with these defects did not differ between cases and controls, suggesting that such bias is unlikely.

Misclassification of cases and controls might have occurred if cardiac defects were not identified or coded. While such misclassification is unlikely to be biased because it is unlikely to be related to FA exposure, nondifferential misclassification could tend to obscure a protective effect of FA on heart anomalies.

Finally, residual confounding is still a possible explanation for not finding a protective effect of FA in this population. In our multivariate model, we adjusted for several factors that are associated with either FA use or cardiac anomalies; nevertheless, other variables might differ between the women who take FA in early pregnancy and women who take no FA during that time. If these differences are related to the presence of heart defects, confounding could explain our findings.

The current literature reflects discussion about the effect of FA on the etiology of DS itself. Polymorphisms of the methylene tetrahydrofolate reductase gene were more prevalent among mothers of children with DS than among control mothers in some studies (Hobbs et al., 2000; James et al., 1999), though other researchers could not confirm this difference (Petersen et al., 2000). Furthermore, Czeizel and Puho (2005) found a decreased risk for DS after periconceptional high-dose FA use in a population-based study. If FA were to protect against DS itself, perhaps the same phenomenon that results in a DS birth despite FA use in pregnancy would also result in a lack of FA protection against heart anomalies. Alternatively, a higher dose might be required

Table 2
Maternal Folic Acid Use in Relation to Cases with Heart Anomalies among Subjects with Down Syndrome

	No. exposed/ nonexposed	OR_{adj}	95% Confidence interval
Controls	84/100		
Cases			
Heart anomalies	110/113	0.946	0.608–1.471
Conotruncal defects	10/10	0.704	0.213–2.323
VSD	40/33	1.456	0.774–2.739
Ostium secundum type ASD	40/33	0.943	0.481–1.847
Endocardial cushion defects	42/43	0.766	0.419–1.367

ORs were adjusted for race, age, education, diabetes, year of birth, center.

to achieve an effect on heart anomalies in DS. Most multivitamin products contain 400 μg of FA; while that dose may be sufficient to reduce cardiac anomaly risks in otherwise normal fetuses, perhaps a larger dose may be needed to protect against development of a heart anomaly when a trisomy 21 is already present.

Findings from previous studies that focused on the effects of certain exogenous maternal factors on the risks of birth defects in DS have been inconsistent, but maternal age and race might play a role. In our study, we found no differences in maternal age between cases and controls. Our findings on maternal race are consistent with Khoury and Erickson (1992) though not with a later study with more accurate rates of heart anomalies (Freeman et al., 1998). This is the first study to investigate the effect of FA on heart anomalies among DS children, and it failed to provide evidence of such an effect. Further studies could improve our understanding of this possible relation by taking into consideration the dose and composition of FA-containing products and possible polymorphisms in folate pathway genes.

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